

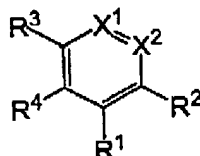
PATENT APPLICATION

Appln No. 10/826,982
 Amdt. Dated July 26, 2006
 Reply to Office Action of April 13, 2006

The listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims

Claim 1. (currently amended). A compound of formula



or a pharmaceutically acceptable salt thereof, wherein

X¹ is C(R²) or N

X² is C(R²) or N; wherein at least one of X¹ and X² is N;

R¹ is C₁₋₈alkyl, C₁₋₄haloalkyl, halo, cyano, nitro, -C(=O)R^b, -C(=O)OR^b, -C(=O)NR^aR^a, -C(=NR^a)NR^aR^a, -OR^a, -OC(=O)R^b, -OC(=O)NR^aR^a, -OC(=O)N(R^a)S(=O)₂R^b, -OC₂₋₆alkylNR^aR^a, -OC₂₋₆alkylOR^a, -SR^a, -S(=O)R^b, -S(=O)₂R^b, -S(=O)₂NR^aR^a, -S(=O)₂N(R^a)C(=O)R^b, -S(=O)₂N(R^a)C(=O)OR^b, -S(=O)₂N(R^a)C(=O)NR^aR^a, -NR^aR^a, -N(R^a)C(=O)R^b, -N(R^a)C(=O)OR^b, -N(R^a)C(=O)NR^aR^a, -N(R^a)C(=NR^a)NR^aR^a, -N(R^a)S(=O)₂R^b, -N(R^a)S(=O)₂NR^aR^a, -NR^aC₂₋₆alkylNR^aR^a or -NR^aC₂₋₆alkylOR^a or C₁₋₈alkyl substituted by 1, 2 or 3 substituents independently selected from cyano, nitro, -C(=O)R^b, -C(=O)OR^b, -C(=O)NR^aR^a, -C(=NR^a)NR^aR^a, -OR^a, -OC(=O)R^b, -OC(=O)NR^aR^a, -OC(=O)N(R^a)S(=O)₂R^b, -OC₂₋₆alkylNR^aR^a, -OC₂₋₆alkylOR^a, -SR^a, -S(=O)R^b, -S(=O)₂R^b, -S(=O)₂NR^aR^a, -S(=O)₂N(R^a)C(=O)R^b, -S(=O)₂N(R^a)C(=O)OR^b, -S(=O)₂N(R^a)C(=O)NR^aR^a, -NR^aR^a, -N(R^a)C(=O)R^b, -N(R^a)C(=O)OR^b, -N(R^a)C(=O)NR^aR^a, -N(R^a)C(=NR^a)NR^aR^a, -N(R^a)S(=O)₂R^b, -N(R^a)S(=O)₂NR^aR^a, -NR^aC₂₋₆alkylNR^aR^a and -NR^aC₂₋₆alkylOR^a;

R² is C₁₋₈alkyl, phenyl, benzyl, R^c, R^f, C₁₋₄alkylR^c, C₁₋₄alkylR^f or R^g;

R³ is phenyl, naphthyl, or a saturated or unsaturated 5- or 6-membered ring heterocycle containing 1-4 heteroatoms selected from N, O and S, wherein no more than 2 of the heteroatoms are O or S, and the heterocycle is substituted by 0, 1 or 2 oxo groups and is optionally fused with a benzo group, any of which are substituted by 0, 1, 2 or 3 substituents selected from C₁₋₈alkyl, C₁₋₄haloalkyl, halo, cyano, nitro, -C(=O)R^b, -C(=O)OR^b, -C(=O)NR^aR^a, -C(=NR^a)NR^aR^a, -OR^a, -OC(=O)R^b, -OC(=O)NR^aR^a, -OC(=O)N(R^a)S(=O)₂R^b, -OC₂₋₆alkylNR^aR^a, -OC₂₋₆alkylOR^a, -SR^a, -S(=O)R^b, -S(=O)₂R^b, -S(=O)₂NR^aR^a, -S(=O)₂N(R^a)C(=O)R^b, -S(=O)₂N(R^a)C(=O)OR^b, -S(=O)₂N(R^a)C(=O)NR^aR^a, -NR^aR^a, -N(R^a)C(=O)R^b, -N(R^a)C(=O)OR^b, -N(R^a)C(=O)NR^aR^a, -N(R^a)C(=NR^a)NR^aR^a, -N(R^a)S(=O)₂R^b, -N(R^a)S(=O)₂NR^aR^a, -NR^aC₂₋₆alkylNR^aR^a and -NR^aC₂₋₆alkylOR^a;

PATENT APPLICATION

Appin No. 10/826,982
 Amdt. Dated July 26, 2006
 Reply to Office Action of April 13, 2006

R^4 is phenyl, naphthyl, or a saturated or unsaturated 5- or 6-membered ring heterocycle containing 1-4 heteroatoms selected from N, O and S, wherein no more than 2 of the heteroatoms are O or S, and the heterocycle is substituted by 0, 1 or 2 oxo groups and is optionally fused with a benzo group, any of which are substituted by 0, 1, 2 or 3 substituents selected from C_{1-8} alkyl, C_{1-4} haloalkyl, halo, cyano, nitro, $-NR^a(C_{1-4}alkylR^f)$, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$;

R^a is independently at each instance H or R^b ;

R^b is independently at each instance C_{1-8} alkyl, phenyl or benzyl;

R^c is independently at each instance a saturated or unsaturated 5-, 6- or 7-membered monocyclic or 6-, 7-, 8-, 9-, 10- or 11-membered bicyclic ring containing 1, 2 or 3 atoms selected from N, O and S, wherein the ring is fused with 0 or 1 benzo groups and 0 or 1 saturated or unsaturated 5-, 6- or 7-membered heterocyclic ring containing 1, 2 or 3 atoms selected from N, O and S; wherein the carbon atoms of the ring are substituted by 0, 1 or 2 oxo groups;

R^d is independently at each instance C_{1-8} alkyl, C_{1-4} haloalkyl, halo, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ or $-NR^aC_{2-6}alkylOR^a$;

R^e is independently at each instance C_{1-6} alkyl substituted by 1, 2 or 3 substituents independently selected from R^d ;

R^f is independently at each instance R^c substituted by 1, 2 or 3 substituents independently selected from R^d ; and

R^g is independently at each instance R^b substituted by 1, 2 or 3 substituents independently selected from R^c , R^f and R^d .

2. (Original) A pharmaceutical composition comprising a compound according to Claim 1 and a pharmaceutically acceptable carrier or diluent.

PATENT APPLICATION

Appln No. 10/826,982
Amdt. Dated July 26, 2006
Reply to Office Action of April 13, 2006

3. (Canceled)

4. (Original) A method of treatment of rheumatoid arthritis, Pagets disease, osteoporosis, multiple myeloma, uveitis, acute or chronic myelogenous leukemia, pancreatic β cell destruction, osteoarthritis, rheumatoid spondylitis, gouty arthritis, inflammatory bowel disease, adult respiratory distress syndrome (ARDS), psoriasis, Crohn's disease, allergic rhinitis, ulcerative colitis, anaphylaxis, contact dermatitis, asthma, muscle degeneration, cachexia, Reiter's syndrome, type I diabetes, type II diabetes, bone resorption diseases, graft vs. host reaction, Alzheimer's disease, stroke, myocardial infarction, ischemia reperfusion injury, atherosclerosis, brain trauma, multiple sclerosis, cerebral malaria, sepsis, septic shock, toxic shock syndrome, fever, myalgias due to HIV-1, HIV-2, HIV-3, cytomegalovirus (CMV), influenza, adenovirus, the herpes viruses or herpes zoster infection in a mammal comprising administering an effective amount of a compound according to Claim 1.

5. (Original) A method of treatment of rheumatoid arthritis comprising administering an effective amount of a compound according to Claim 1.

6. (Original) A method of lowering plasma concentrations of either or both TNF- α and IL-1 comprising administering an effective amount of a compound according to Claim 1.

7. (Original) A method of lowering plasma concentrations of either or both IL-6 and IL-8 comprising administering an effective amount of a compound according to Claim 1.

8. (Original) A method of treatment of a pain disorder in a mammal comprising administering an effective amount of a compound according to Claim 1.

9. (Original) The manufacture of a medicament comprising an effective amount of a compound according to Claim 1.

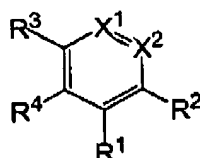
10. (Canceled)**11. (Canceled)**

PATENT APPLICATION

Appln No. 10/826,982
 Amdt. Dated July 26, 2006
 Reply to Office Action of April 13, 2006

12. (New) The compound of claim 1 wherein one of X^1 and X^2 is N and the other of one of X^1 and X^2 is C(R^2).

13. (New) A compound of formula



or a pharmaceutically acceptable salt thereof, wherein

X^1 is C(R^2) or N

X^2 is C(R^2) or N; wherein at least one of X^1 and X^2 is N;

R^1 is C_{1-8} alkyl, C_{1-4} haloalkyl, halo, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylINR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylINR^aR^a$ or $-NR^aC_{2-6}alkylOR^a$ or C_{1-8} alkyl substituted by 1, 2 or 3 substituents independently selected from cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylINR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylINR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$;

R^2 is C_{1-8} alkyl, phenyl, benzyl, R^c , R^f , $C_{1-4}alkylR^c$, $C_{1-4}alkylR^f$ or R^g ;

R^3 is phenyl, naphthyl, or a saturated or unsaturated 5- or 6-membered ring heterocycle containing 1-4 heteroatoms selected from N, O and S, wherein no more than 2 of the heteroatoms are O or S, and the heterocycle is substituted by 0, 1 or 2 oxo groups and is optionally fused with a benzo group, any of which are substituted by 0, 1, 2 or 3 substituents selected from C_{1-8} alkyl, C_{1-4} haloalkyl, halo, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylINR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylINR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$;

PATENT APPLICATION

Appln No. 10/826,982

Amdt. Dated July 26, 2006

Reply to Office Action of April 13, 2006

R^4 is naphthyl, or a saturated or unsaturated 5- or 6-membered ring heterocycle containing 1-4 heteroatoms selected from N, O and S, wherein no more than 2 of the heteroatoms are O or S, and the heterocycle is substituted by 0, 1 or 2 oxo groups and is optionally fused with a benzo group, any of which are substituted by 0, 1, 2 or 3 substituents selected from C_{1-6} alkyl, C_{1-4} haloalkyl, halo, cyano, nitro, $-NR^a(C_{1-4}alkylR^f)$, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$;

R^a is independently at each instance H or R^b ;

R^b is independently at each instance C_{1-6} alkyl, phenyl or benzyl;

R^c is independently at each instance a saturated or unsaturated 5-, 6- or 7-membered monocyclic or 6-, 7-, 8-, 9-, 10- or 11-membered bicyclic ring containing 1, 2 or 3 atoms selected from N, O and S, wherein the ring is fused with 0 or 1 benzo groups and 0 or 1 saturated or unsaturated 5-, 6- or 7-membered heterocyclic ring containing 1, 2 or 3 atoms selected from N, O and S; wherein the carbon atoms of the ring are substituted by 0, 1 or 2 oxo groups;

R^d is independently at each instance C_{1-6} alkyl, C_{1-4} haloalkyl, halo, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ or $-NR^aC_{2-6}alkylOR^a$;

R^e is independently at each instance C_{1-6} alkyl substituted by 1, 2 or 3 substituents independently selected from R^d ;

R^f is independently at each instance R^c substituted by 1, 2 or 3 substituents independently selected from R^d ; and

R^g is independently at each instance R^b substituted by 1, 2 or 3 substituents independently selected from R^c , R^f and R^d .

14. (New) The compound of claim 13 wherein one of X^1 and X^2 is N and the other of one of X^1 and X^2 is $C(R^2)$.

PATENT APPLICATION

AppIn No. 10/826,982
 Amdt. Dated July 26, 2006
 Reply to Office Action of April 13, 2006

15. (New) The compound of claim 13 wherein R^4 is a pyridine or pyrimidine ring, optionally substituted by 0, 1, 2 or 3 substituents selected from C_{1-8} alkyl, C_{1-4} haloalkyl, halo, cyano, nitro, $-NR^a(C_{1-4}alkylR^f)$, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$.

16. (New) A pharmaceutical composition comprising a compound according to Claim 13 and a pharmaceutically acceptable carrier or diluent.

17. (New) A method of treatment of rheumatoid arthritis comprising administering an effective amount of a compound according to Claim 13.

18. (New) A method of lowering plasma concentrations of either or both TNF- α and IL-1 comprising administering an effective amount of a compound according to Claim 13.

19. (New) A method of lowering plasma concentrations of either or both IL-6 and IL-8 comprising administering an effective amount of a compound according to Claim 13.

20. (New) A method of treatment of a pain disorder in a mammal comprising administering an effective amount of a compound according to Claim 13.

21. (New) The manufacture of a medicament comprising an effective amount of a compound according to Claim 13.